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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Mike Meller Examiner #: 69404 Date: 3/25/03
Art Unit: 1654 Phone Number 30 8-4236 Serial Number: 10/056,666
Mail Box and Bldg/Room Location: 10A03 Results Format Preferred (circle): PAPER DISK E-MAIL

11D13

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Materials for lysosome Modulation and methods...

Inventors (please provide full names): Ben A. Bahr

Earliest Priority Filing Date: 10/30/2000

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search. claim 9 with respect to using the specific compound of clm. 13, if no hits, then expand to broader lysosomal comps. as shown in cl 11.

RECEIVED MAR 25 2003 TC1600/2900 CHEM/BIOTECH (STIC)

****

STAFF USE ONLY

Searcher: Point of Contact: Alexandra Waclawiw
Searcher Phone #: Technical Info. Specialist CM1 6A02 Tel: 308-4491
Searcher Location:
Date Searcher Picked Up: 3-27
Date Completed: 3-31
Searcher Prep & Review Time: 15
Clerical Prep Time:
Online Time: 42

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#) 3
Bibliographic
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

STN $ 54806 615
Dialog
Questel/Orbit 42
Dr.Link
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (8-01)

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=> d his

     (FILE 'HCAPLUS' ENTERED AT 09:45:53 ON 31 MAR 2003)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 09:46:23 ON 31 MAR 2003
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L1             STR
L2   (      3362)SEA FILE=REGISTRY SSS FUL L1
L3             STR
L4             3 SEA FILE=REGISTRY SUB=L2 SSS FUL L3
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     FILE 'HCAPLUS' ENTERED AT 09:47:40 ON 31 MAR 2003
L5            61 S L4
L6         18188 S LYSOSOM?
L7            15 S L5 AND L6
L8          4140 S NEURODEGENER?
L9         81338 S (NERVE OR NERVOUS OR BRAIN ) (L) (DISEASE# OR DISORDER?)
L10        82480 S L9 OR L8
L11            4 S L5 AND L10
L12           17 S L7 OR L11
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=> fil reg
FILE 'REGISTRY' ENTERED AT 09:49:35 ON 31 MAR 2003
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   30 MAR 2003  HIGHEST RN 500991-80-0
DICTIONARY FILE UPDATES:  30 MAR 2003  HIGHEST RN 500991-80-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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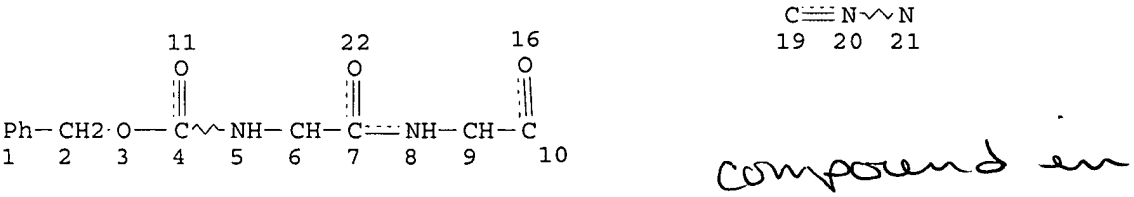

compound en Claim 13

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE
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L3                STR
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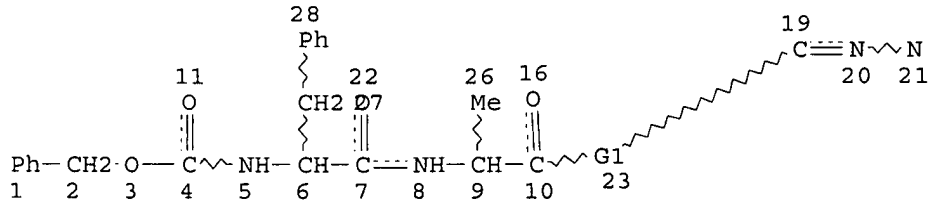

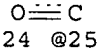

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 22

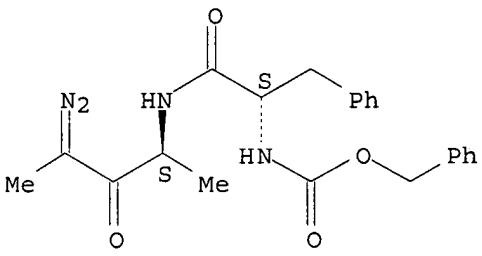
STEREO ATTRIBUTES: NONE
L4 3 SEA FILE=REGISTRY SUB=L2 SSS FUL L3

100.0% PROCESSED 79 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

=> d l4 ide can 1-4

L4 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 120240-73-5 REGISTRY
CN Carbamic acid, [2-[(3-diazo-1-methyl-2-oxobutyl)amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H24 N4 O4
SR CA
LC STN Files: CA, CAPLUS

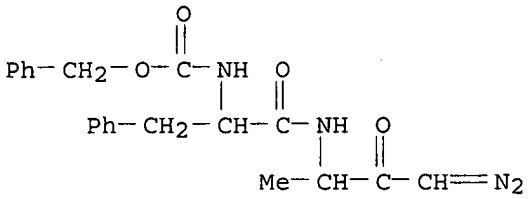
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 110:188336

L4 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 81719-36-0 REGISTRY
CN Carbamic acid, [2-[(3-diazo-1-methyl-2-oxopropyl)amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H22 N4 O4
LC STN Files: CA, CAPLUS, USPATFULL



5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 116:250833

REFERENCE 2: 105:39101

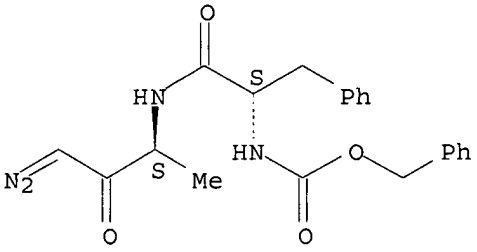
REFERENCE 3: 104:16871

REFERENCE 4: 103:22931

REFERENCE 5: 96:195703

L4 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 71732-53-1 REGISTRY
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [2-[(3-diazo-1-methyl-2-oxopropyl)amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]-
FS STEREOSEARCH
MF C21 H22 N4 O4
LC STN Files: CA, CAPLUS, CASREACT, CHEMCATS, MEDLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



56 REFERENCES IN FILE CA (1962 TO DATE)
56 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:66184

REFERENCE 2: 137:88476

REFERENCE 3: 136:147461

REFERENCE 4: 136:79329

REFERENCE 5: 135:89548

REFERENCE 6: 134:54110

REFERENCE 7: 133:261535

REFERENCE 8: 132:347872

REFERENCE 9: 132:343360

REFERENCE 10: 131:110938

=> fil hcaplus
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FILE COVERS 1907 - 31 Mar 2003 VOL 138 ISS 14
FILE LAST UPDATED: 30 Mar 2003 (20030330/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que nos l12
L1 STR
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L3 STR
L4 3 SEA FILE=REGISTRY SUB=L2 SSS FUL L3
L5 61 SEA FILE=HCAPLUS ABB=ON PLU=ON L4
L6 18188 SEA FILE=HCAPLUS ABB=ON PLU=ON LYSOSOM?/OBI
L7 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND L6
L8 4140 SEA FILE=HCAPLUS ABB=ON PLU=ON NEURODEGENER?/OBI
L9 81338 SEA FILE=HCAPLUS ABB=ON PLU=ON (NERVE/OBI OR NERVOUS/OBI OR
BRAIN/OBI) (L) (DISEASE#/OBI OR DISORDER?/OBI)
L10 82480 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 OR L8
L11 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND L10
L12 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L7 OR L11

=> d .ca l12 1-17

L12 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:540253 HCAPLUS
DOCUMENT NUMBER: 137:88476
TITLE: **Lysosome**-modulating compounds, and
therapeutic and other methods of use

INVENTOR(S): Bahr, Ben A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002094958	A1	20020718	US 2001-56666	20011029

PRIORITY APPLN. INFO.: US 2000-244327P P 20001030
US 2000-254778P P 20001211

OTHER SOURCE(S): MARPAT 137:88476

AB Compds. and methods of use thereof for modulating lysosome function are disclosed. Also disclosed is use of the compds. to treat neurodegenerative events and to study lysosomal function. Compds. of the invention include cathepsin antagonists. Specifically claimed compds. include e.g. benzyloxycarbonyl-Phe-Ala-diazomethylketone.

IC ICM A61K038-06
ICS A61K038-05; A61K031-655; A61K031-397; A61K031-445; A61K031-401
NCL 514018000
CC 1-11 (Pharmacology)
Section cross-reference(s): 9
ST cathepsin antagonist **lysosome** modulator **neurodegeneration** treatment; peptide deriv **lysosome** modulator **neurodegeneration** treatment
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GluR1 subunit; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT **Nerve, disease**
Nervous system
(degeneration; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Peptides, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Esters, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diazoacetyl peptidyl alkyl esters; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Brain
(hippocampus; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**lysosomal**; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Animal tissue culture
Dendrite (neuron)
Drug delivery systems
Lysosome
Microtubule
Nervous system agents
Synapse

(**lysosome**-modulating compds., and therapeutic and other methods of use)
IT Synaptophysin
Tau factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**lysosome**-modulating compds., and therapeutic and other methods of use)
IT Biological transport
(markers; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Brain
(neocortex; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Cytoprotective agents
(neuroprotectants; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Ketones, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidyl diazomethylketones; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Semicarbazones
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidyl; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Synapse
(postsynapse; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT Synapse
(presynapse; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT 9004-08-4, Cathepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; **lysosome**-modulating compds., and therapeutic and other methods of use)
IT 9025-26-7, Cathepsin D 9047-22-7, Cathepsin B 71965-46-3, Cathepsin S
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**lysosome**-modulating compds., and therapeutic and other methods of use)
IT 65178-14-5 **71732-53-1** 77180-09-7 118253-05-7 442663-68-5 442663-69-6
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**lysosome**-modulating compds., and therapeutic and other methods of use)
IT 19982-08-2, Memantine
RL: PAC (Pharmacological activity); BIOL (Biological study)
(**lysosome**-modulating compds., and therapeutic and other methods of use)

L12 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107685 HCAPLUS
DOCUMENT NUMBER: 136:147461
TITLE: Model for Alzheimer's disease and other **neurodegenerative** diseases
INVENTOR(S): Lynch, Gary; Bi, Xiaoning
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010768	A2	20020207	WO 2001-US23894	20010731
WO 2002010768	A3	20030103		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002048746	A1	20020425	US 2001-917789	20010731

PRIORITY APPLN. INFO.: US 2000-222060P P 20000731
US 2001-283352P P 20010413

AB The present invention provides a model for studying the development of, and/or pathologies assocd. with, neurodegenerative diseases, and agents that can alter such development and/or pathologies. The model of the invention is esp. useful as an Alzheimer's disease model. The model of the invention provides brain cells and a method for increasing neurodegenerative disease characteristics in such cells. Neurodegenerative disease characteristics are induced by various means, such as introduction of neurofibrillary tangles, phosphorylated tau, or tau fragments; modulation with cytokines; inducing microglial reactions; conversion of p35 to p25; or altering protein kinases by selectively increasing the concn. of cathepsin D to an effective level, and/or by lowering the concn. of cholesterol in such cells. The model also provides a method of reversing such effects, by inhibiting cysteine protease and mitogen-activated kinase activity, and esp., by inhibiting calpain, and/or MAP kinase.

IC ICM G01N033-68
CC 9-2 (Biochemical Methods)
Section cross-reference(s): 1, 14
ST Alzheimer disease **neurodegenerative** disease model
IT Apolipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E4; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)
IT Apolipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)
IT Lipopolysaccharides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bacterial; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)
IT Alzheimer's disease
Anti-Alzheimer's agents
Disease models
Human
Inflammation
Lysosome
Mouse
Neurofibrillary tangle

(cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Interleukin 1.beta.
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT **Nervous** system
(degeneration; cellular models of Alzheimer's **disease** and other **neurodegenerative diseases**)

IT **Brain**
(entorhinal cortex; cellular models of Alzheimer's **disease** and other **neurodegenerative diseases**)

IT **Brain**
(hippocampus; cellular models of Alzheimer's **disease** and other **neurodegenerative diseases**)

IT **Brain**
(hypothalamus; cellular models of Alzheimer's **disease** and other **neurodegenerative diseases**)

IT Neuroglia
(microglia; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT **Brain**
(neocortex; cellular models of Alzheimer's **disease** and other **neurodegenerative diseases**)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p25; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p35; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Phosphorylation, biological
(protein; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Transferrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.tau.-transferrins; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Amyloid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(.beta.-; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT 65178-14-5 **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

IT 54-05-7, Chloroquine 57-88-5, Cholesterol, biological studies
9025-26-7, Cathepsin D 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L
73573-88-3, Mevastatin 75330-75-5, Lovastatin 78990-62-2, Calpain
79902-63-9, Simvastatin 81093-37-0, Pravastatin 93957-54-1,
Fluvastatin 109511-58-2, U0126 111694-09-8, Tau kinase 134523-00-5,
Atorvastatin 142243-02-5, MAP kinase 145599-86-6, Cerivastatin
147014-96-8, Cdk5 kinase 152121-47-6, SB203580 167869-21-8, PD98059
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(cellular models of Alzheimer's disease and other **neurodegenerative** diseases)
IT 110044-82-1, Calpain inhibitor I
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cellular models of Alzheimer's disease and other **neurodegenerative** diseases)
IT 37353-41-6, Cysteine protease
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; cellular models of Alzheimer's disease and other **neurodegenerative** diseases)

L12 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:508062 HCAPLUS
DOCUMENT NUMBER: 135:89548
TITLE: An in vitro assay method for the study of brain aging
INVENTOR(S): Lynch, Gary S.; Bednarski, Eric; Ribak, Charles E.; Gall, Christine M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001007854	A1	20010712	US 1997-787784	19970122
US 6447988	B2	20020910		

PRIORITY APPLN. INFO.: US 1997-787784 19970122
AB Cultured brain slices are treated with a free radical generator, in the presence of a lysosomal enzyme inhibitor (specifically an inhibitor of two cathepsins). The treated brain slices rapidly develop autofluorescent lipofuscin granules-a universal feature of brain aging. Other correlates of the aged brain are also induced by this treatment, thereby providing an in vitro model for (1) the study of brain aging; (2) assessment of anti-brain aging drugs; and (3) therapeutics directed at the clin. condition referred to as neuronal ceroid-lipofuscinosis.
IC ICM A01N001-00
ICS A01N001-02; A01N037-18; A61K038-00; A61K038-16; G01N033-53; G01N033-537; G01N033-543; A61K031-70; A01N043-04
NCL 514006000
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 14
IT Aging, animal
Animal tissue culture
Brain
Culture media
Dendrite (neuron)
Drug screening
Gamma ray
Hypoxia, animal
Lysosome
Mammal (Mammalia)
Neuroglia
Oxidizing agents
Reducing agents
Simulation and Modeling, physicochemical
UV radiation
(An in vitro assay method for the study of brain aging)

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**lysosomal** inhibitors; An in vitro assay method for the study of brain aging)
IT 50-81-7, Ascorbic acid, biological studies 58-27-5, Menadione 80-15-9, Cumene hydroperoxide 475-38-7, Naphthazarine 4685-14-7, Paraquat 7720-78-7, Ferrous sulfate 7722-84-1, Hydrogen peroxide, biological studies 9001-37-0, Glucose oxidase 9002-17-9, Xanthine oxidase 9076-44-2, Chymostatin 11062-77-4, Superoxide 55123-66-5, Leupeptin 65178-14-5 66701-25-5, E-64 **71732-53-1** 94047-28-6, Cystatins 110044-82-1, Calpain inhibitor I 110115-07-6, Calpain inhibitor II 114014-15-2 134448-10-5D, CA-074, Me ester
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(An in vitro assay method for the study of brain aging)

L12 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:688091 HCAPLUS
DOCUMENT NUMBER: 133:261535
TITLE: Methods for treating **neurodegenerative** disorders using aspartyl protease inhibitors
INVENTOR(S): Ellman, Jonathan A.; Lynch, Gary; Kuntz, Irwin D.; Bi, Xiaoning; Lee, Christina E.; Skillman, A. Geoffrey; Haque, Tasir
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056335	A1	20000928	WO 2000-US7804	20000324
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1178800	A1	20020213	EP 2000-916643	20000324
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539260	T2	20021119	JP 2000-606240	20000324

PRIORITY APPLN. INFO.: US 1999-125958P P 19990324
WO 2000-US7804 W 20000324

OTHER SOURCE(S): MARPAT 133:261535
AB Non-peptide aspartyl protease inhibitors, methods for modulating the processing of an amyloid precursor protein, methods for modulating the processing of a .tau.-protein, and methods for treating neurodegenerative diseases are provided.
IC ICM A61K031-445
ICS A61K031-40; A61K031-16
CC 1-11 (Pharmacology)
Section cross-reference(s): 27
ST aspartyl protease inhibitor **neurodegenerative** disease treatment; amyloid precursor protein processing modulation aspartyl protease inhibitor; tau protein processing modulation aspartyl protease inhibitor

IT Body fluid
Cerebrospinal fluid
Combinatorial library
Nervous system agents
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative disorders**)

IT Amyloid precursor proteins
Tau factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT **Nervous** system
(degeneration; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative disorders**)

IT **Brain**
(entorhinal cortex; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative disorders**)

IT **Brain**
(hippocampus; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative disorders**)

IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.-; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 9025-26-7, Cathepsin D
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 54-05-7, Chloroquine **71732-53-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 211114-74-8P 211114-75-9P 211114-76-0P 211114-94-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 192069-75-3 192069-78-6 192069-80-0 192069-83-3 192069-84-4
192069-91-3 192069-95-7 192069-96-8 192069-98-0 192069-99-1
192070-00-1 211114-70-4 211114-71-5 211114-77-1 211114-78-2
211114-81-7 211114-83-9 211114-84-0 211114-85-1 211114-86-2
211114-87-3 211114-88-4 211114-89-5 211114-90-8 211115-00-3
227031-04-1 227031-05-2 227031-06-3 227031-07-4 227031-08-5
227031-09-6 227031-10-9 227031-11-0 227031-12-1 227031-13-2
296780-76-2 296780-77-3 296780-78-4 296780-79-5 296780-80-8

296780-81-9 296780-82-0 296780-83-1 296780-84-2 296780-85-3
296780-87-5 296780-88-6 296780-89-7 296780-90-0 296780-92-2
296780-93-3 296780-95-5 296780-96-6 296780-98-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 78169-47-8, Aspartyl protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 213458-69-6DP, resin-coupled 213458-69-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 60456-21-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:335259 HCAPLUS
DOCUMENT NUMBER: 132:343360
TITLE: A method for treating tissue damaged from ischemia by using a peptidyl diazomethyl ketone
INVENTOR(S): Seyfried, Donald M.; Anagli, John
PATENT ASSIGNEE(S): Research Corporation Technologies, Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027418	A2	20000518	WO 1999-US26718	19991112
WO 2000027418	A3	20000908		
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1131082	A2	20010912	EP 1999-963889	19991112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002529422	T2	20020910	JP 2000-580647	19991112
US 6458760	B1	20021001	US 1999-439705	19991112

PRIORITY APPLN. INFO.: US 1998-108049P P 19981112
WO 1999-US26718 W 19991112
OTHER SOURCE(S): MARPAT 132:343360
AB The present invention relates to a method for treating tissue damage caused by ischemia in a patient which comprises administering to said

patient a therapeutically effective amt. of a peptidyl diazomethyl ketone which is an inhibitor of cathepsin B or cathepsin L, but which is not as an effective inhibitor of calpain relative to cathepsin B or cathepsin L or both. For example, CBZ-Phe-Ser(OBz)CHN2 (CP-1) was prepd. from O-benzyl-L-serine and N-.alpha.-benzyloxycarbonyl-L-phenylalanine N-hydroxysuccinimide in a yield of 80%. When given i.v. to Wistar rats, CP-1 decreased an infarct size at concns. of 10, 50, and 250 .mu.M, but not at 2 .mu.M.

IC ICM A61K038-05
ICS A61K038-06; A61K038-55; A61P025-00; A61P009-10

CC 1-12 (Pharmacology)
Section cross-reference(s): 34

IT **Nervous** system
(**disease**; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT **Brain**, **disease**
Heart, disease
(ischemia; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT **Brain**, **disease**
(stroke; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT 65178-14-5P **71732-53-1P** 85680-09-7P 85680-10-0P
85680-12-2P 114014-15-2P 114014-16-3P 114480-14-7P 116614-38-1P
116614-45-0P 116641-98-6P 116641-99-7P 142070-20-0P 154992-43-5P
268741-03-3P 268741-04-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

L12 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:449386 HCAPLUS
DOCUMENT NUMBER: 131:70860
TITLE: Brain aging assay
INVENTOR(S): Lynch, Gary S.; Bednarski, Eric; Ribak, Charles E.; Gall, Christine M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9934781	A1	19990715	WO 1998-US1140	19980108
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862457	A1	19990726	AU 1998-62457	19980108

PRIORITY APPLN. INFO.: WO 1998-US1140 19980108

AB Cultured brain slices are treated with a free radical generator, in the

presence of a lysosomal enzyme inhibitor (specifically an inhibitor of two cathepsins). The treated brain slices rapidly develop autofluorescent lipofuscin granules - a universal feature of brain aging. Other correlates of the aged brain are also induced by this treatment, thereby providing an in vitro model for (1) the study of brain aging; (2) assessment of anti-brain aging drugs; and (3) therapeutics directed at the clin. condition referred to as neuronal ceroid-lipofuscinosis.

IC ICM A61K009-44
ICS C12N005-00; C12N005-02; C12Q001-00; G01N001-30; G01N033-48

CC 9-16 (Biochemical Methods)

IT Aging, animal
Animal tissue culture
Brain
Culture media
Cytoplasm
Dendrite (neuron)
Drugs
Electron microscopes
Gamma ray
Hypoxia, animal
Lysosome
Mammal (Mammalia)
Neuroglia
Neuronal ceroid lipofuscinosis
Oxidizing agents
Reducing agents
UV radiation
(brain aging assay)

IT **71732-53-1**
RL: ANT (Analyte); ANST (Analytical study)
(brain aging assay)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:687413 HCAPLUS
DOCUMENT NUMBER: 130:90677
TITLE: Experimentally induced **lysosomal** dysfunction disrupts processing of hypothalamic releasing factors
AUTHOR(S): Bi, Xiaoning; Pinkstaff, Jason; Nguyen, Kelly; Gall, Christine M.; Lynch, Gary
CORPORATE SOURCE: Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA, 92697-3800, USA
SOURCE: Journal of Comparative Neurology (1998), 401(3), 382-394
CODEN: JCNEAM; ISSN: 0021-9967
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have shown that exptl. induced lysosomal dysfunction elicits various features of aging in the cortical telencephalon. The present study used cultured slices to test if: (1) it causes similar changes in the hypothalamus, and/or (2) modifies the processing of two releasing factors important to aging. A 2-day exposure to N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone (ZPAD), a selective inhibitor of cathepsins B and L, triggered a pronounced increase in the nos. of lysosomes in the ventromedial and dorsomedial nuclei, and in lateral hypothalamus. Continued incubation with the inhibitor for 3-12 days resulted in the spread of endosomes-lysosomes into dendrites and, in the lateral hypothalamus, the formation of massive, lysosome-filled

expansions of neuronal processes (meganeurites). These effects did not occur in the arcuate nucleus, making it the first region so far examd. in which lysosomal proliferation is not initiated by hydrolase inhibitors. Despite this, a dense plexus of axons and terminals in the median eminence was partially depleted of growth hormone releasing hormone (GHRH) within 48 h after addn. of ZPAD. Moreover, the inhibitor caused axonal GHRH to become collected into large puncta, an effect highly suggestive of a partial failure in axonal transport. GHRH mRNA levels were not greatly affected by 6 days of ZPAD exposure, indicating that reduced expression did not play a major role in the peptide changes seen at 48 h. Similar but less pronounced immunocytochem. changes were recorded for the somatostatin system in the arcuate and periventricular nucleus. It is concluded that lysosome dysfunction: (1) has different consequences for the arcuate nucleus than other brain regions, and (2) disrupts transport of hypothalamic releasing factors. The potential significance of the results to endocrine senescence is discussed.

CC 2-5 (Mammalian Hormones)

ST **lysosome** dysfunction hypothalamic releasing factor processing

IT Organelle
(endocytic vesicle; **lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT Brain
(hypothalamus, arcuate nucleus; **lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT Brain
(hypothalamus, median eminence; **lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT Brain
(hypothalamus; **lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT Aging, animal
Biological transport
Dendrite (neuron)
Lysosome
(**lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

IT 9034-39-3, Somatoliberin 51110-01-1, Somatostatin-14
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**lysosomal** dysfunction induction disrupts hypothalamic releasing factor processing)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:195118 HCAPLUS

DOCUMENT NUMBER: 122:3257

TITLE: In vitro embryotoxicity of the cysteine proteinase inhibitors benzyloxycarbonyl-phenylalanine-alanine-diazomethane (Z-Phe-Ala-CHN2) and benzyloxycarbonyl-phenylalanine-phenylalanine-diazomethane (Z-Phe-Phe-CHN2)

AUTHOR(S): Ambroso, Jeffrey L.; Harris, Craig

CORPORATE SOURCE: Department Environmental Industrial Health, Univ. Michigan, Ann Arbor, MI, 48109-2029, USA

SOURCE: Teratology (1994), 50(3), 214-28
CODEN: TJADAB; ISSN: 0040-3709
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study makes use of whole embryo culture to investigate the potential embryotoxicity of Z-Phe-Ala-CHN2 and Z-Phe-Phe-CHN2, two low mol. wt., active site-directed and irreversible inhibitors of the lysosomal cysteine proteinases. Peptidyl diazomethanes are the most specific inhibitors available for lysosomal cysteine proteinases and can be hypothesized to interrupt visceral yolk sac(VYS)-mediated nutrition during early organogenesis. When added directly to the culture medium of gestational day 10-11 rat conceptuses, both compds. inhibited lysosomal cysteine proteinase activity in the VYS in a concn.-dependent fashion that correlated with the degree of embryotoxicity obsd. Z-Phe-Ala-CHN2 and Z-Phe-Phe-CHN2 were also found to increase the protein content of the VYS, even though all other conceptal growth parameters decreased. This effect was dependent on the serum content of the culture medium and the exposure time. Histol. examn. of Z-Phe-Ala-CHN2-treated conceptuses revealed a dramatic increase in the size and no. of vacuoles in the VYS endoderm epithelium, suggestive of inhibition of VYS proteolysis. At the same time, excessive cell death was obsd. throughout the neuroepithelium and in specific regions of the mesenchyme of the corresponding embryos. This cell death manifested morphol. characteristics of apoptosis and could be detected by supravital staining with Nile Blue Sulfate. These findings provide addnl. evidence in support of the hypothesis that lysosomal cysteine proteinases play a crit. role in VYS-mediated histiotrophic nutrition and suggest that peptidyldiazometanes may be useful in further characterization of these enzymes. The possible direct effects of these inhibitors on embryonic cells and the relationships between interruption of VYS-mediated nutritional processes and embryonic cell death are discussed.

CC 4-6 (Toxicology)

IT Apoptosis
Embryo
Lysosome
Teratogenesis
Teratogens
(cysteine proteinase inhibitors embryotoxicity)

IT 65178-14-5 **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cysteine proteinase inhibitors embryotoxicity)

L12 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:212318 HCAPLUS
DOCUMENT NUMBER: 120:212318

TITLE: Leishmania mexicana: proteinase activities and megasomes in axenically cultivated amastigote-like forms

AUTHOR(S): Pral, Elizabeth M. F.; Bijovsky, A. Tania; Balanco, J. M. F.; Alfieri, Silvia C.
CORPORATE SOURCE: Inst. Cienc. Biomed., Univ. Sao Paulo, Sao Paulo, 05508-900, Brazil

SOURCE: Experimental Parasitology (1993), 77(1), 62-73
CODEN: EXPAAA; ISSN: 0014-4894
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Proteinase activities and megasomes were examd. in axenically cultivated amastigote-like forms, freshly isolated lesion amastigotes, and promastigotes. Megasomes were absent in promastigotes and present in both

amastigote stages, but they seemed to be less numerous and more homogeneous in cultured amastigote-like forms. Contrasting with the poor detection of proteinase activities in promastigote lysates, both types of amastigotes shared multiple proteinases, which were classified in two groups: (a) 60 to >100 kDa, o-phenanthroline-sensitive activities; and (b) 23- to 40-kDa cysteine proteinases, of which those resolving as 35- to 40-kDa bands in gelatin gels were more clearly visualized in lysates of cultured amastigote-like forms. Incubation of both kinds of amastigotes with 0.25 to 1.0 .mu.M of either Z-Phe-AlaCHN2 or Z-Tyr-AlaCHN2 selectively inactivated cysteine proteinases, but not the 35- to 40-kDa activities, which, again, were detected with higher intensity in cultured amastigote-like forms. The expression of the 35- to 40-kDa proteinases progressively increased when promastigotes were allowed to transform into amastigote-like forms or when lesion amastigotes were incubated at 34.degree.C for different time periods prior to exposure to Z-Phe-AlaCHN2; activities comparable to those of amastigote-like forms were attained within 24 to 48 h. The activities resistant to Z-Phe-AlaCHN2 in vivo were fully inhibited by E-64 or Z-Phe-AlaCHN2 during gelatin digestion, suggesting that the 35- to 40-kDa proteinases were mainly inactive before cell lysis. The presence of cycloheximide (at 10, 50, and 100 .mu.g/mL) during the pulse with Z-Phe-AlaCHN2 abolished the 35- to 40-kDa activities of lesion amastigotes and significantly reduced gelatin digestion by the similar enzymes of cultured amastigote-like forms. In the latter, the 35- to 40-kDa proteinases were no more detected when cycloheximide was given 60 min prior to Z-Phe-AlaCHN2. The results indicate higher rates of synthesis of the 35- to 40-kDa enzymes, and the existence of a more representative pool of inactive enzyme precursors, in cultured amastigote-like forms.

CC 10-3 (Microbial, Algal, and Fungal Biochemistry)

IT **Lysosome**
(megasome, of Leishmania mexicana amastigote-like forms)

IT **71732-53-1** 114515-99-0
RL: BIOL (Biological study)
(cysteine proteinases of Leishmania mexicana amastigote-like forms differential sensitivity to)

L12 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:508969 HCAPLUS
DOCUMENT NUMBER: 117:108969
TITLE: Inhibition of cysteine proteinases in **lysosomes** and whole cells
AUTHOR(S): Wilcox, Donna; Mason, Robert W.
CORPORATE SOURCE: Dep. Biochem. Nutr., Virginia Polytech. Inst. and State Univ., Blacksburg, VA, 24061, USA
SOURCE: Biochemical Journal (1992), 285(2), 495-502
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of cysteine proteinases have been used extensively to dissect the roles of these proteinases in cells. Surprisingly though, little work has been performed to demonstrate unequivocally that the inhibitors reach and inactivate their target proteinases in cell culture or in vivo. In the present study, the permeability of lysosomes and whole cells was studied. Benzyloxycarbonyl (Z)-[125I]iodo-Tyr-Ala-diazomethane (CHN2), an inhibitor of cathepsins L and B, has been shown to label active forms of these enzymes in lysosomes and whole cells. The ability of other cysteine proteinase inhibitors to block this labeling has been used to indicate the permeation of these compds. All the inhibitors were able to block labeling of Z-[125I]iodo-Tyr-Ala-CHN2 in lysosomal exts. In intact lysosomes or cells, however, only N-[N-(L-3-trans-ethoxycarbonyloxirane-2-

carbonyl)-L-leucyl]-3-methylbutylamine (E-64d), Z-Tyr-Ala-CHN2, Z-Phe-Ala-CHN2-carbonyl)-L-leucyl]amino-4-guanidinobutane (E-64), and leupeptin were unable to block labeling by Z-[125I]iodo-Tyr-Ala-CHN2 in lysosomes or in cells. The ability to block labeling in lysosomes is an indication of the ability of the inhibitor to diffuse across membranes. Thus E-64 and leupeptin do not readily permeate membranes, and therefore their uptake into cells probably only occurs via pinocytosis.

CC 13-7 (Mammalian Biochemistry)
Section cross-reference(s): 7

ST cysteine proteinase inhibitor permeation **lysosome** cell; cathepsin inhibitor permeation **lysosome**; leupeptin permeation cell **lysosome**

IT Leupeptins
RL: BIOL (Biological study)
(cysteine proteinase inhibition by, in **lysosomes** and cells, permeation through membrane in relation to)

IT Animal cell
Lysosome
(cysteine proteinase inhibitors permeation into, degree of inhibition in relation to)

IT Biological transport
(permeation, of cysteine proteinase inhibitors into **lysosomes** and cells, degree of inhibition in relation to)

IT 65178-14-5 66701-25-5 **71732-53-1** 76684-89-4 88321-09-9 114515-99-0
RL: BIOL (Biological study)
(cysteine proteinase inhibition by, in **lysosomes** and cells, permeation through membrane in relation to)

IT 9047-22-7, Cathepsin B 37353-41-6, Cysteine proteinase 60616-82-2, Cathepsin L
RL: BIOL (Biological study)
(inhibition of, in **lysosomes** and animal cells, permeability of inhibitors effect on)

L12 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:136378 HCAPLUS
DOCUMENT NUMBER: 112:136378
TITLE: Insoluble disulfide crosslinked polypeptides accumulate in the functionally compromised **lysosomes** of fibroblasts treated with the cysteine protease inhibitor E 64
AUTHOR(S): Doherty, Fergus J.; Osborn, Natasha U.; Wassell, Julie A.; Laszlo, Lajos; Mayer, R. John
CORPORATE SOURCE: Med. Sch., Univ. Nottingham, Nottingham, NG7 2UH, UK
SOURCE: Experimental Cell Research (1989), 185(2), 506-18
CODEN: ECREAL; ISSN: 0014-4827
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mouse fibroblasts (3T3-L1 cells) accumulate pulse-labeled long-lived polypeptides in detergent- and salt-insol. aggregates when chased in the presence of inhibitors of lysosomal cysteine cathepsins, including E 64. Proteins found in the detergent- and salt-insol. fraction include polypeptides which are disulfide crosslinked. E 64-induced polypeptide aggregates cofractionate with lysosomal enzyme markers on d. gradients and are found in multivesicular dense bodies which by electron microscopy appear to be engaged in microautophagy. The results are discussed in relation to the possible role of polypeptide aggregation in the sequestration or trapping of cytoplasmic proteins by the lysosomal system.

CC 13-2 (Mammalian Biochemistry)

ST disulfide crosslink polypeptide **lysosome** fibroblast; cysteine

proteinase inhibitor fibroblast
IT Fibroblast
(disulfide-contg. polypeptide accumulation in **lysosomes** of, cysteine proteinase inhibitors induction of)
IT **Lysosome**
(disulfide-contg. polypeptide accumulation in, of fibroblast, cysteine proteinase inhibitors effect on)
IT Proteins, specific or class
RL: BIOL (Biological study)
(disulfide-contg., insol., accumulation of, in fibroblast **lysosomes**, cysteine proteinase inhibitors induction of)
IT 54-05-7, Chloroquine 12125-02-9, Ammonium chloride, biological studies 65178-14-5 66701-25-5, E 64 **71732-53-1**
RL: BIOL (Biological study)
(disulfide-contg. polypeptide accumulation in fibroblast **lysosomes** response to)
IT 37353-41-6, Cysteine proteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, insol. disulfide-contg. polypeptides accumulation in fibroblast **lysosomes** response to)

L12 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:569914 HCAPLUS
DOCUMENT NUMBER: 111:169914
TITLE: Interaction of **lysosomal** cysteine proteinases with .alpha.2-macroglobulin: conclusive evidence for the endopeptidase activities of cathepsins B and H
AUTHOR(S): Mason, Robert W.
CORPORATE SOURCE: Dep. Biochem., Strangeways Res. Lab., Cambridge, CB1 4RN, UK
SOURCE: Archives of Biochemistry and Biophysics (1989), 273(2), 367-74
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The lysosomal cysteine proteinases, cathepsins B, H, and L, were all shown to bind to .alpha.2-macroglobulin. The bound enzymes remained active against low-mol.-wt. synthetic substrates and bound the active-site-directed inhibitor, benzyloxycarbonyl-[125I]Tyr-Ala-diazomethane. Binding of the radiolabeled inhibitor to high-mol.-wt. protein on SDS polyacrylamide gels indicated that a proportion of the enzymes was covalently bound to .alpha.2-macroglobulin. Cleavage fragments of .alpha.2-macroglobulin of Mr 92,000 and 86,000 were seen for cathepsins B, H, and L, indicating cleavage in the bait region. Binding and cleavage were obsd. for both single-chain and 2-chain forms of cathepsin B from human, ox, and pig livers, showing that all active forms of cathepsins B, H, and L are endopeptidases.
CC 7-3 (Enzymes)
ST cathepsin binding alpha2 macroglobulin endopeptidase activity; **lysosome** cathepsin endopeptidase activity
IT **Lysosome**
(cathepsins of human and lab. animal, endopeptidase activity of)
IT Michaelis constant
(of cathepsin, of human and lab. animal **lysosome** for synthetic peptides)
IT Kinetics, enzymic
(of inhibition, of cathepsins of human and lab. animal **lysosome** by synthetic peptide)
IT Macroglobulins

RL: BIOL (Biological study)
(.alpha.2-, cathepsin of human and lab. animal **lysosome** binding of, endopeptidase activity of enzyme in relation to)
IT **71732-53-1**
RL: BIOL (Biological study)
(cathepsins of human and lab. animal **lysosomes** inhibition by, kinetics of)
IT 9047-22-7, Cathepsin B 60748-73-4, Cathepsin H
RL: BIOL (Biological study)
(endopeptidase activity of, of human **lysosome**, .alpha.2-macroglobulin binding in relation to)
IT 65147-22-0 65286-27-3 88937-61-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with cathepsins of human and lab. animal **lysosome**, kinetics of)

L12 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:529576 HCAPLUS
DOCUMENT NUMBER: 111:129576
TITLE: Plasmodium falciparum: inhibitors of **lysosomal** cysteine proteinases inhibit a trophozoite proteinase and block parasite development
AUTHOR(S): Rosenthal, Philip J.; McKerrow, James H.; Rasnick, David; Leech, James H.
CORPORATE SOURCE: Dep. Med., San Francisco Gen. Hosp., San Francisco, CA, 94110, USA
SOURCE: Molecular and Biochemical Parasitology (1989), 35(2), 177-83
CODEN: MBIPDR; ISSN: 0166-6851
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The biochem. properties of the trophozoite cysteine proteinase closely resembled those of the lysosomal cysteine proteinases cathepsin B and cathepsin L. The trophozoite proteinase had a pH optimum of 5.5-6.0, near that of both lysosomal proteinases, and it was efficiently inhibited by highly specific diazomethylketone and fluoromethylketone inhibitors of cathepsin B and cathepsin L. The trophozoite proteinase preferred peptide substrates with arginine adjacent to hydrophobic amino acids, as does cathepsin L. Micromolar concns. of the fluoromethylketone inhibitor Z-Phe-Ala-CH2F (where Z = benzyloxycarbonyl) blocked the degrdn. of Hb in the trophozoite food vacuole and prevented parasite multiplication. In previous studies much higher concns. of the inhibitor were not toxic for mice. The results provide addnl. evidence that the 28-kDa trophozoite proteinase is a food vacuole hemoglobinase and suggest that specific inhibitors of the enzyme may have potential as antimalarial drugs.
CC 7-3 (Enzymes)
Section cross-reference(s): 1
IT 65178-14-5 **71732-53-1** 105637-38-5
RL: BIOL (Biological study)
(cysteine proteinase of Plasmodium falciparum inhibition by, kinetics of, malaria therapy in relation to)

L12 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:107530 HCAPLUS
DOCUMENT NUMBER: 104:107530
TITLE: A group-specific inhibitor of **lysosomal** cysteine proteinases selectively inhibits both proteolytic degradation and presentation of the antigen dinitrophenyl-poly-L-lysine by guinea pig accessory cells to T cells

AUTHOR(S): Buus, Soeren; Werdelin, Ole
CORPORATE SOURCE: Univ. Inst. Pathol., Univ. Copenhagen, Copenhagen, DK-2100, Den.
SOURCE: Journal of Immunology (1986), 136(2), 452-8
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB With the aid of highly specific inhibitors of proteinases, the role of proteolysis in the presentation of antigens by guinea pig accessory cells was examd. The proteinase inhibitor benzyloxycarbonyl-phenylalanylalanine-diazomethyl-ketone, which selectively inhibits cysteine proteinases, was used to block this set of enzymes in cultured cells. The selective inhibition of the cysteine proteinases of antigen-presenting cells causes a profound inhibition of both the proteolytic degrdn. and the presentation of the synthetic antigen dinitrophenyl-poly-L-lysine. In contrast, the presentation of another synthetic antigen, the copolymer of L-glutamic acid and L-alanine, was enhanced by the same inhibitor. Another inhibitor, pepstatin A, which selectively blocks aspartic proteinases, did not block the presentation of dinitrophenyl-poly-L-lysine. The results identify cysteine proteinases, probably lysosomal, as one of the groups of enzymes involved in antigen processing.

CC 15-2 (Immunochemistry)
Section cross-reference(s): 7

ST antigen processing cysteine proteinase **lysosome**

IT **Lysosome**
(cysteine proteinases of, in antigen presentation by accessory cells)

IT Antigens
RL: PROC (Process)
(presentation of, by accessory cells, **lysosomal** cysteine proteinases in)

IT Lymphocyte
(T-, antigen presentation to, by accessory cells, **lysosomal** cysteine proteinases in)

IT Macrophage
(accessory cell, antigen presentation by, **lysosomal** cysteine proteinases in)

IT Polyamides, biological studies
RL: BIOL (Biological study)
(poly(amino acids), accessory cells presentation of antigenic, **lysosomal** cysteine proteinases in)

IT Tuberculins
RL: BIOL (Biological study)
(purified protein derivs., accessory cells presentation of antigenic, **lysosomal** cysteine proteinases in)

IT 25104-18-1D, dinitrophenyl conjugates 26655-93-6 31325-39-0
RL: BIOL (Biological study)
(accessory cells presentation of antigenic, **lysosomal** cysteine proteinases in)

IT 26305-03-3 **71732-53-1**
RL: BIOL (Biological study)
(antigen presentation by accessory cells inhibition by)

IT 37353-41-6
RL: BIOL (Biological study)
(of **lysosome**, in antigen presentation by accessory cells)

L12 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:586807 HCAPLUS
DOCUMENT NUMBER: 101:186807
TITLE: Species variations amongst **lysosomal** cysteine proteinases

AUTHOR(S): Kirschke, Heidrun; Locnikar, Pavel; Turk, Vito
CORPORATE SOURCE: Physiol.-Chem. Inst., Martin-Luther-Univ. Halle-Wittenberg, Halle/Saale, DDR-4020, Ger. Dem. Rep.
SOURCE: FEBS Letters (1984), 174(1), 123-7
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Properties of cathepsin L from rat liver lysosomes were compared with those of a similar enzyme, cathepsin S from beef spleen. Major characteristics of cathepsin L are the high activity against Z-Phe-Arg-methylcoumarylamide (Z = benzyloxycarbonyl) and sensitivity to the fast-reacting irreversible inhibitor Z-Phe-Phe-diazomethane. In contrast, cathepsin S hydrolyzes Z-Phe-Arg-methylcoumarylamide only slowly, and Z-Phe-Phe-diazomethane cannot be regarded as a potent inhibitor of this enzyme. The differences in the substrate specificity of cathepsin L from rat liver and cathepsin S from beef spleen are discussed in comparison with the substrate specificity of cathepsin B from rat and human liver and beef spleen.

CC 7-3 (Enzymes)

ST cysteine proteinase **lysosome** specificity species; cathepsin **lysosome** specificity species

IT **Lysosome**
(cathepsin of, of human and lab. animal, species difference in)

IT **71732-53-1**
RL: BIOL (Biological study)
(cathepsin inhibition by, species specificity in)

IT 37353-41-6
RL: BIOL (Biological study)
(of **lysosome** of human and lab. animal, specificity of, species differences in)

IT 60616-82-2
RL: BIOL (Biological study)
(specificity of, of liver **lysosome**, species in relation to)

IT 71965-46-3
RL: BIOL (Biological study)
(specificity of, of spleen **lysosome**, species in relation to)

L12 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:420350 HCAPLUS
DOCUMENT NUMBER: 99:20350
TITLE: The thiol proteinase inhibitors, Z-Phe-PheCHN2 and Z-Phe-AlaCHN2, inhibit **lysosomal** protein degradation in isolated rat hepatocytes
AUTHOR(S): Grinde, Bjoern
CORPORATE SOURCE: Zool. Inst., Univ. Oslo, Oslo, Norway
SOURCE: Biochimica et Biophysica Acta (1983), 757(1), 15-20
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects on protein metab. of Z-Phe-PheCHN2 and Z-Phe-AlaCHN2 (where Z = benzyloxycarbonyl) were examd. in isolated rat hepatocytes. The 2 thiol proteinase inhibitors caused a drastic redn. in the degrdn. of both endogenous and endocytosed (asialofetuin) protein. The inhibition was not additive to that of the lysosomotropic base MeNH2, indicating that Z-Phe-PheCHN2 and Z-Phe-AlaCHN2 only affect lysosomal degrdn. At high concns. (0.1-1 mM) both inhibitors reduced protein synthesis strongly. This finding indicates nonspecific/toxic effects, which may limit the usefulness of the inhibitors.

CC 13-7 (Mammalian Biochemistry)

ST thiol protease protein metab **lysosome** hepatocyte
IT Proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, by **lysosomal** hepatocyte, thiol protease in relation to)
IT **Lysosome**
(protein metab. by, of hepatocyte, thiol proteinase in relation to)
IT Liver, metabolism
(hepatocyte, protein metab. by **lysosome** of, thiol protease in relation to)
IT 37353-41-6
RL: BIOL (Biological study)
(in protein metab., by **lysosomal** hepatocyte)
IT 65178-14-5 **71732-53-1**
RL: BIOL (Biological study)
(protein metab. by **lysosomal** hepatocyte in relation to)

L12 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:176747 HCAPLUS
DOCUMENT NUMBER: 98:176747
TITLE: The regulation of proteolysis in normal fibroblasts as they approach confluence. Evidence for the participation of the **lysosomal** system
AUTHOR(S): Cockle, Sheena M.; Dean, Roger T.
CORPORATE SOURCE: Sch. Biol. Sci., Brunel Univ., Uxbridge, UB8 3PH, UK
SOURCE: Biochemical Journal (1982), 208(3), 795-800
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English
AB NH4Cl, leupeptin (I), benzyloxycarbonyl-Phe-Ala-diazomethane (II), and pepstatin (III) all inhibited the degrdn. of intracellular proteins in Swiss 3T3 mouse and normal human fibroblasts in both the exponential and stationary (confluent) growth phases in nutritionally complete conditions. The increase in proteolysis normally occurring as cells approached confluence could be completely blocked by NH4Cl, II, or by III in the presence of I. These results suggest that the lysosomal system is responsible for the regulation of proteolysis at confluence and further confirm its role in basal proteolysis in growing cells.
CC 13-2 (Mammalian Biochemistry)
Section cross-reference(s): 6
ST **lysosome** fibroblast confluence proteolysis regulation
IT Fibroblast
(confluent, **lysosomal** regulation of proteolysis in)
IT Proteins
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrolysis of, in confluent fibroblasts, **lysosomal** regulation of)
IT **Lysosome**
(regulation of proteolysis in confluent fibroblasts in relation to)
IT 12125-02-9, biological studies **71732-53-1**
RL: BIOL (Biological study)
(proteolysis in confluent fibroblasts inhibition by)

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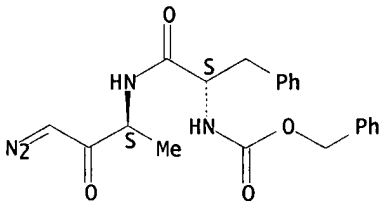
L39 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:171378 CAPLUS
DOCUMENT NUMBER: 138:66184
TITLE: Cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii
AUTHOR(S): Shaw, Michael K.; Roos, David S.; Tilney, Lewis G.
CORPORATE SOURCE: Department of Biology, University of Pennsylvania, Philadelphia, PA, 19104-6018, USA
SOURCE: Microbes and Infection (2002), 4(2), 119-132
CODEN: MCINFS; ISSN: 1286-4579
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A no. of cysteine and serine protease inhibitors blocked the intracellular growth and replication of Toxoplasma gondiitachyzoites. Most of these inhibitors caused only minor alterations to parasite morphol. irresp. of the effects on the host cells. However, three, cathepsin inhibitor III, TPCK and subtilisin inhibitor III, caused extensive swelling of the secretory pathway of the parasite (i.e. the ER, nuclear envelope, and Golgi complex), caused the breakdown of the parasite surface membrane, and disrupted rhoptry formation. The disruption of the secretory pathway is consistent with the post-translational processing of secretory proteins in Toxoplasma, and with the role of proteases in the maturation/activation of secreted proteins in general. Interestingly, while all parasites in an individual vacuole (the clonal progeny of a single invading parasite) were similarly affected, parasites in different vacuoles in the same host cell showed different responses to these inhibitors. Such observations imply that there are major differences in the biochem./physiol. between tachyzoites within different vacuoles and argue that adverse effects on the host cell are not always responsible for changes in the parasite. Treatment of established parasites also leads to an accumulation of abnormal materials in the parasitophorous vacuole implying that materials deposited into the vacuole normally undergo proteolytic modification or degrdn. Despite the often extensive morphol. changes, nothing resembling lysosomal bodies was seen in any treated parasites, consistent with previous observations showing that mother cell organelles are not recycled by any form of autophagic-lysosomal degrdn., although the question of how the parasite recycles these organelles remains unanswered.

IT 71732-53-1
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

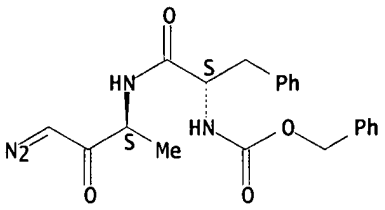


CC 1-5 (Pharmacology)
ST cysteine serine protease inhibitor secretory Toxoplasma gondii
IT Endoplasmic reticulum
Golgi apparatus
Parasite

Toxoplasma gondii
(cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
IT Cell nucleus
(envelope; cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
IT Organelle
(rhoptry; cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
IT 9004-07-3, Chymotrypsin 37259-58-8, Serine protease 37353-41-6, Cysteine protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
IT 59-61-0, DCI 26305-03-3, Pepstatin A 35172-59-9 55123-66-5, Leupeptin 65178-14-5 66701-25-5, E-64 **71732-53-1**
76684-89-4, E-64c 96551-81-4, Arphamenine A 110115-07-6 180313-87-5
180313-89-7
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cysteine and serine protease inhibitors block intracellular development and disrupt the secretory pathway of Toxoplasma gondii)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:799047 CAPLUS
DOCUMENT NUMBER: 136:79329
TITLE: Analysis of antimalarial synergy between bestatin and endoprotease inhibitors using statistical response-surface modelling
AUTHOR(S): Gavigan, Clare S.; Machado, Stella G.; Dalton, John P.; Bell, Angus
CORPORATE SOURCE: Department of Microbiology, Trinity College, Dublin, 2, Ire.
SOURCE: Antimicrobial Agents and Chemotherapy (2001), 45(11), 3175-3181
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pathway of Hb degrdn. by erythrocytic stages of the human malarial parasite Plasmodium falciparum involves initial cleavages of globin chains, catalyzed by several endoproteases, followed by liberation of amino acids from the resulting peptides, probably by aminopeptidases. This pathway is considered a promising chemotherapeutic target, esp. in view of the antimalarial synergy obsd. between inhibitors of aspartyl and cysteine endoproteases. We have applied response-surface modeling to assess antimalarial interactions between endoprotease and aminopeptidase inhibitors using cultured P. falciparum parasites. The synergies obsd. were consistent with a combined role of endoproteases and aminopeptidases in Hb catabolism in this organism. As synergies between antimicrobial agents are often inferred without proper statistical anal., the model used may be widely applied in studies of antimicrobial drug interactions.
IT **71732-53-1**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anal. of antimalarial synergy between bestatin and endoprotease inhibitors using statistical response-surface modeling)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-5 (Pharmacology)
ST antimalarial synergy bestatin endoprotease inhibitor modeling
IT Antimalarials
Plasmodium falciparum
Simulation and Modeling, biological
(anal. of antimalarial synergy between bestatin and endoprotease inhibitors using statistical response-surface modeling)
IT Protein degradation
(role of Plasmodium falciparum aminopeptidase in concert with aspartyl and cysteine endoproteases in Hb degrdn)
IT Hemoglobins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(role of Plasmodium falciparum aminopeptidase in concert with aspartyl and cysteine endoproteases in Hb degrdn)
IT Drug interactions
(synergistic; anal. of antimalarial synergy between bestatin and endoprotease inhibitors using statistical response-surface modeling)
IT 39324-30-6, Pepstatin 58970-76-6, Bestatin 66701-25-5, E-64 71732-53-1
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anal. of antimalarial synergy between bestatin and endoprotease inhibitors using statistical response-surface modeling)
IT 9031-94-1, Aminopeptidase 37353-41-6, Cysteine proteinase 78169-47-8, Aspartyl proteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(role of Plasmodium falciparum aminopeptidase in concert with aspartyl and cysteine endoproteases in Hb degrdn)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:335259 CAPLUS
DOCUMENT NUMBER: 132:343360
TITLE: A method for treating tissue damaged from ischemia by using a peptidyl diazomethyl ketone
INVENTOR(S): Seyfried, Donald M.; Anagli, John
PATENT ASSIGNEE(S): Research Corporation Technologies, Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027418	A2	20000518	WO 1999-US26718	19991112
WO 2000027418	A3	20000908		
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1131082	A2	20010912	EP 1999-963889	19991112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002529422	T2	20020910	JP 2000-580647	19991112

US 6458760 B1 20021001 US 1999-439705 19991112
PRIORITY APPLN. INFO.: US 1998-108049P P 19981112
WO 1999-US26718 W 19991112
OTHER SOURCE(S): MARPAT 132:343360

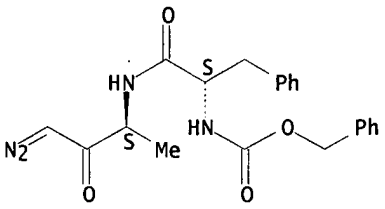
AB The present invention relates to a method for treating tissue damage caused by ischemia in a patient which comprises administering to said patient a therapeutically effective amt. of a peptidyl diazomethyl ketone which is an inhibitor of cathepsin B or cathepsin L, but which is not as an effective inhibitor of calpain relative to cathepsin B or cathepsin L or both. For example, CBZ-Phe-Ser(OBz)CHN2 (CP-1) was prepd. from O-benzyl-L-serine and N-.alpha.-benzyloxycarbonyl-L-phenylalanine N-hydroxysuccinimide in a yield of 80%. When given i.v. to Wistar rats, CP-1 decreased an infarct size at concns. of 10, 50, and 250 .mu.M, but not at 2 .mu.M.

IT **71732-53-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

RN 71732-53-1 CAPLUS

CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A61K038-05
ICS A61K038-06; A61K038-55; A61P025-00; A61P009-10

CC 1-12 (Pharmacology)
Section cross-reference(s): 34

ST peptidyl diazomethyl ketone cathepsin inhibitor antiischemic

IT Nervous system
(disease; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT Brain, disease
Heart, disease
(ischemia; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT Anti-ischemic agents
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT Dipeptides
Tripeptides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT Brain, disease
(stroke; peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT 65178-14-5P **71732-53-1P** 85680-09-7P 85680-10-0P
85680-12-2P 114014-15-2P 114014-16-3P 114480-14-7P 116614-38-1P
116614-45-0P 116641-98-6P 116641-99-7P 142070-20-0P 154992-43-5P
268741-03-3P 268741-04-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic**

use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT 78990-62-2, Calpain 186322-81-6, Caspase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peptidyl diazomethyl ketones as inhibitors of cathepsin B or L, but not calpain or caspase for ischemia treatment)

IT 2577-48-2 3397-32-8 4726-96-9, O-Benzyl-L-serine 7801-71-0 18822-59-8 69538-46-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

IT 118252-98-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptidyl diazomethyl ketones as inhibitors of cathepsin B or L for ischemia treatment)

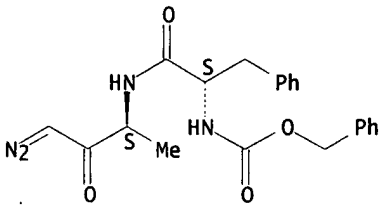
L39 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:199087 CAPLUS
DOCUMENT NUMBER: 131:110938
TITLE: Cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei
AUTHOR(S): Troeberg, Linda; Morty, Rory E.; Pike, Robert N.; Lonsdale-Eccles, John D.; Palmer, James T.; McKerrow, James H.; Coetzer, Theresa H. T.
CORPORATE SOURCE: Department of Biochemistry, University of Natal (Pietermaritzburg), Scottsville, 3209, S. Afr.
SOURCE: Experimental Parasitology (1999), 91(4), 349-355
CODEN: EXPAAA; ISSN: 0014-4894
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Trypanosoma brucei brucei is a causative agent of bovine trypanosomiasis (nagana), a disease of considerable economic significance in much of Africa. Here we report investigations on the effects of various irreversible cysteine proteinase inhibitors, including vinyl sulfones (VS), peptidyl chloromethylketones (CMK), diazomethylketones, and fluoromethyl ketones, on the major lysosomal cysteine proteinase (trypanopain-Tb) of T. b. brucei and on in vitro-cultured bloodstream forms of the parasite. Many of the tested inhibitors were trypanocidal at low micromolar concns. Methyl piperazine urea-Phe-homoPhe-VS was the most effective trypanocidal agent, killing 50% of test populations at a work ing concn. of 0.11 .mu.M, while carbobenzoxy-Phe-Phe-CMK was the most trypanocidal of the methylketones with an IC50 of 3.6 .mu.M. Labeling of live and lysed T. b. brucei with biotinylated inhibitor derivs. suggests that trypanopain-Tb is the likely intracellular target for these inhibitors. Kinetic anal. of the inhibition of purified trypanopain-Tb by the inhibitors showed that most had kass values in the 106 M-1 s-1 range. We conclude that cysteine proteinase inhibitors have potential as trypanocidal agents and that a major target of these compds. is the lysosomal enzyme trypanopain-Tb. (c) 1999 Academic Press.

IT 71732-53-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei)

RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-5 (Pharmacology)
Section cross-reference(s): 10
ST trypanocidal cysteine proteinase inhibitor Trypanosoma brucei
IT Trypanosoma brucei brucei
Trypanosomicides
(cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei)
IT 402-71-1 2364-87-6 26049-94-5 41658-44-0 52780-79-7 60525-17-9 65144-34-5 65178-14-5 **71732-53-1** 90302-94-6 105637-38-5 130143-19-0 211060-81-0 213822-40-3 213822-41-4 213822-42-5 213822-44-7 233277-97-9 233277-98-0 233277-99-1 233278-00-7 233278-01-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei)
IT 37353-41-6, Cysteine proteinase 179466-48-9, Trypanopain-Tb
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:199083 CAPLUS
DOCUMENT NUMBER: 131:110937
TITLE: Trypanosoma rangeli: killing of bloodstream forms in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2
AUTHOR(S): Scory, Stefan; Caffrey, Conor R.; Stierhof, York-Dieter; Ruppel, Andreas; Steverding, Dietmar
CORPORATE SOURCE: Abteilung Parasitologie, Hyg.-Inst., Ruprecht-Karls-Univ., Heidelberg, D-69120, Germany
SOURCE: Experimental Parasitology (1999), 91(4), 327-333
CODEN: EXPAAA; ISSN: 0014-4894
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Trypanosoma brucei: Killing of bloodstream forms in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN 2. Cysteine proteinases were tested for their suitability as targets for chemotherapy of sleeping sickness using the peptidyl inhibitor Z-Phe-Ala-diazomethyl ketone (Z-Phe-Ala-CHN2). In vitro, the inhibitory concn. of Z-Phe-Ala-CHN;2 required to reduce the growth rate by 50% was 400 times lower for culture-adapted bloodstream forms of Trypanosoma brucei than for a mouse myeloma cell line. At an inhibitor concn. of 10 M the parasites were lysed within 48 h of incubation. Parasitemia of mice infected with T. brucei decreased to undetectable levels for 3 days following treatment with 250 mg/kg Z-Phe-Ala-CHN2 on days 3 to 6 after infection. Although parasitemia returned thereafter to control levels, infected mice treated with the inhibitor survived approx. twice as long as those treated with placebo. Z-Phe-Ala-CHN2 inhibited proteinolysis in lysosomes in vitro and almost completely blocked cysteine proteinase activity in vivo. The

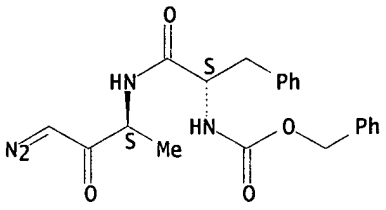
results demonstrate the importance of cysteine proteinase activity for survival of T. brucei and suggest that such activity is an appropriate target for antitrypanosomal chemotherapy. (c) 1999 Academic Press.

IT **71732-53-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(killing of bloodstream forms of Trypanosoma rangeli in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2)

RN 71732-53-1 CAPLUS

CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-5 (Pharmacology)
Section cross-reference(s): 10, 14

ST antitrypanosomal ZPheAlaCHN trypanosomiasis parasitemia Trypanosoma rangeli

IT Parasitemia
Trypanosoma brucei
Trypanosoma rangeli
Trypanosomicides
(killing of bloodstream forms of Trypanosoma rangeli in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2)

IT Infection
(trypanosomiasis; killing of bloodstream forms of Trypanosoma rangeli in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2)

IT **71732-53-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(killing of bloodstream forms of Trypanosoma rangeli in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2)

IT 37353-41-6, Cysteine proteinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(killing of bloodstream forms of Trypanosoma rangeli in vitro and in vivo by the cysteine proteinase inhibitor Z-Phe-Ala-CHN2)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/30/2000

MELLER

=> d ibib abs hitstr ind l35

L35 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:540253 CAPLUS
DOCUMENT NUMBER: 137:88476
TITLE: Lysosome-modulating compounds, and therapeutic and other methods of use
INVENTOR(S): Bahr, Ben A
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

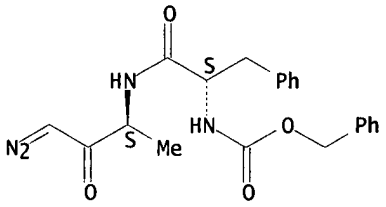
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002094958	A1	20020718	US 2001-56666	20011029
PRIORITY APPLN. INFO.:			US 2000-244327P P	20001030
			US 2000-254778P P	20001211

OTHER SOURCE(S): MARPAT 137:88476

AB Compds. and methods of use thereof for modulating lysosome function are disclosed. Also disclosed is use of the compds. to treat **neurodegenerative** events and to study lysosomal function. Compds. of the invention include cathepsin antagonists. Specifically claimed compds. include e.g. benzyloxycarbonyl-Phe-Ala-diazomethylketone.

IT 71732-53-1
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lysosome-modulating compds., and therapeutic and other methods of use)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A61K038-06
ICS A61K038-05; A61K031-655; A61K031-397; A61K031-445; A61K031-401
NCL 514018000
CC 1-11 (Pharmacology)
Section cross-reference(s): 9
ST cathepsin antagonist lysosome modulator **neurodegeneration** treatment; peptide deriv lysosome modulator **neurodegeneration** treatment
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GluR1 subunit; lysosome-modulating compds., and therapeutic and other methods of use)
IT Nerve, disease
Nervous system, disease
(degeneration; lysosome-modulating compds., and therapeutic and other methods of use)
IT Peptides, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; lysosome-modulating compds., and therapeutic and other

methods of use)
IT Esters, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diazoacetyl peptidyl alkyl esters; lysosome-modulating compds., and therapeutic and other methods of use)
IT Brain
(hippocampus; lysosome-modulating compds., and therapeutic and other methods of use)
IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lysosomal; lysosome-modulating compds., and therapeutic and other methods of use)
IT Animal tissue culture
Dendrite (**neuron**)
Drug delivery systems
Lysosome
Microtubule
Nervous system agents
Synapse
(lysosome-modulating compds., and therapeutic and other methods of use)
IT Synaptophysin
Tau factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lysosome-modulating compds., and therapeutic and other methods of use)
IT Biological transport
(markers; lysosome-modulating compds., and therapeutic and other methods of use)
IT Brain
(neocortex; lysosome-modulating compds., and therapeutic and other methods of use)
IT Cytoprotective agents
(**neuroprotectants**; lysosome-modulating compds., and therapeutic and other methods of use)
IT Ketones, biological studies
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidyl diazomethylketones; lysosome-modulating compds., and therapeutic and other methods of use)
IT Semicarbazones
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidyl; lysosome-modulating compds., and therapeutic and other methods of use)
IT Synapse
(postsynapse; lysosome-modulating compds., and therapeutic and other methods of use)
IT Synapse
(presynapse; lysosome-modulating compds., and therapeutic and other methods of use)
IT 9004-08-4, Cathepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; lysosome-modulating compds., and therapeutic and other methods of use)
IT 9025-26-7, Cathepsin D 9047-22-7, Cathepsin B 71965-46-3, Cathepsin S
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lysosome-modulating compds., and therapeutic and other methods of use)
IT 65178-14-5 **71732-53-1** 77180-09-7 118253-05-7 442663-68-5
442663-69-6
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lysosome-modulating compds., and therapeutic and other methods of use)
IT 19982-08-2, Memantine
RL: PAC (Pharmacological activity); BIOL (Biological study)
(lysosome-modulating compds., and therapeutic and other methods of use)

=> d ibib abs hitstr ind l35 2-8

L35 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:107685 CAPLUS
DOCUMENT NUMBER: 136:147461
TITLE: Model for **Alzheimer**'s disease and other **neurodegenerative** diseases
INVENTOR(S): Lynch, Gary; Bi, Xiaoning
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010768	A2	20020207	WO 2001-US23894	20010731
WO 2002010768	A3	20030103		
WO 2002010768	C2	20030710		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002048746	A1	20020425	US 2001-917789	20010731
EP 1315971	A2	20030604	EP 2001-956047	20010731

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

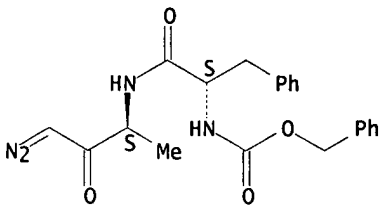
PRIORITY APPLN. INFO.:
US 2000-222060P P 20000731
US 2001-283352P P 20010413
WO 2001-US23894 W 20010731

AB The present invention provides a model for studying the development of, and/or pathologies assocd. with, **neurodegenerative** diseases, and agents that can alter such development and/or pathologies. The model of the invention is esp. useful as an **Alzheimer**'s disease model. The model of the invention provides brain cells and a method for increasing **neurodegenerative** disease characteristics in such cells. **Neurodegenerative** disease characteristics are induced by various means, such as introduction of **neurofibrillary** tangles, phosphorylated tau, or tau fragments; modulation with cytokines; inducing microglial reactions; conversion of p35 to p25; or altering protein kinases by selectively increasing the concn. of cathepsin D to an effective level, and/or by lowering the concn. of cholesterol in such cells. The model also provides a method of reversing such effects, by inhibiting cysteine protease and mitogen-activated kinase activity, and esp., by inhibiting calpain, and/or MAP kinase.

IT **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)

RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM G01N033-68
CC 9-2 (Biochemical Methods)
Section cross-reference(s): 1, 14
ST **Alzheimer** disease **neurodegenerative** disease model
IT Apolipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E4; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Apolipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Lipopolysaccharides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bacterial; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT **Alzheimer**'s disease
Anti-**Alzheimer**'s agents
Disease models
Human
Inflammation
Lysosome
Mouse
Neurofibrillary tangle
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Interleukin 1.beta.
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Nervous system, disease
(degeneration; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Brain
(entorhinal cortex; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Brain
(hippocampus; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Brain
(hypothalamus; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT **Neuroglia**
(microglia; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Brain
(neocortex; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p25; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p35; cellular models of **Alzheimer**'s disease and other

neurodegenerative diseases)
IT Phosphorylation, biological
(protein; cellular models of **Alzheimer**'s disease and other **neur degenerative** diseases)
IT Transferrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.tau.-transferrins; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Amyloid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(.beta.-; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT 65178-14-5 71732-53-1
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT 54-05-7, Chloroquine 57-88-5, Cholesterol, biological studies
9025-26-7, Cathepsin D 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L
73573-88-3, Mevastatin 75330-75-5, Lovastatin 78990-62-2, Calpain
79902-63-9, Simvastatin 81093-37-0, Pravastatin 93957-54-1,
Fluvastatin 109511-58-2, U0126 111694-09-8, Tau kinase 134523-00-5,
Atorvastatin 142243-02-5, MAP kinase 145599-86-6, Cerivastatin
147014-96-8, Cdk5 kinase 152121-47-6, SB203580 167869-21-8, PD98059
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT 110044-82-1, Calpain inhibitor I
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)
IT 37353-41-6, Cysteine protease
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; cellular models of **Alzheimer**'s disease and other **neurodegenerative** diseases)

L35 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:508062 CAPLUS
DOCUMENT NUMBER: 135:89548
TITLE: An in vitro assay method for the study of brain aging
INVENTOR(S): Lynch, Gary S.; Bednarski, Eric; Ribak, Charles E.; Gall, Christine M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

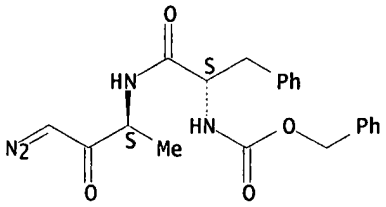
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001007854	A1	20010712	US 1997-787784	19970122
US 6447988	B2	20020910		

PRIORITY APPLN. INFO.: US 1997-787784 19970122

AB Cultured brain slices are treated with a free radical generator, in the presence of a lysosomal enzyme inhibitor (specifically an inhibitor of two cathepsins). The treated brain slices rapidly develop autofluorescent lipofuscin granules-a universal feature of brain aging. Other correlates of the aged brain are also induced by this treatment, thereby providing an in vitro model for (1) the study of brain aging; (2) assessment of anti-brain aging drugs; and (3) therapeutics directed at the clin. condition referred to as **neuronal** ceroid-lipofuscinosis.
IT 71732-53-1

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(An in vitro assay method for the study of brain aging)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A01N001-00
ICS A01N001-02; A01N037-18; A61K038-00; A61K038-16; G01N033-53; G01N033-537; G01N033-543; A61K031-70; A01N043-04
NCL 514006000
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 14
ST brain aging lipofuscin lysozyme inhibitor model drug screening
IT Aging, animal
Animal tissue culture
Brain
Culture media
Dendrite (**neuron**)
Drug screening
Gamma ray
Hypoxia, animal
Lysosome
Mammal (Mammalia)
Neuroglia
Oxidizing agents
Reducing agents
Simulation and Modeling, physicochemical
UV radiation
(An in vitro assay method for the study of brain aging)
IT Radicals, biological studies
Salts, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(An in vitro assay method for the study of brain aging)
IT Lipofuscins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(autofluorescent; An in vitro assay method for the study of brain aging)
IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lysosomal inhibitors; An in vitro assay method for the study of brain aging)
IT Nerve
(**neuron**; An in vitro assay method for the study of brain aging)
IT Cytoplasm
(perikaryal; An in vitro assay method for the study of brain aging)
IT Amyloid
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(.beta.-, fragments 1-42/43 and 25-35; An in vitro assay method for the study of brain aging)
IT 9047-22-7, Cathepsin b 60616-82-2, Cathepsin l

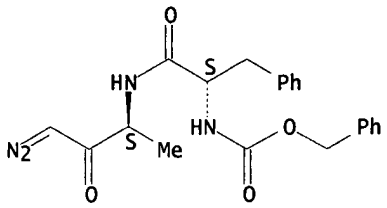
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(An in vitro assay method for the study of brain aging)
IT 50-81-7, Ascorbic acid, biological studies 58-27-5, Menadione 80-15-9, Cumene hydroperoxide 475-38-7, Naphthazarine 4685-14-7, Paraquat 7720-78-7, Ferrous sulfate 7722-84-1, Hydrogen peroxide, biological studies 9001-37-0, Glucose oxidase 9002-17-9, Xanthine oxidase 9076-44-2, Chymostatin 11062-77-4, Superoxide 55123-66-5, Leupeptin 65178-14-5 66701-25-5, E-64 71732-53-1 94047-28-6, Cystatins 110044-82-1, Calpain inhibitor I 110115-07-6, Calpain inhibitor II 114014-15-2 134448-10-5D, CA-074, Me ester
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(An in vitro assay method for the study of brain aging)
IT 9001-92-7, Protease
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inhibitor, pig leukocyte cysteine; An in vitro assay method for the study of brain aging)

L35 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:688091 CAPLUS
DOCUMENT NUMBER: 133:261535
TITLE: Methods for treating **neurodegenerative** disorders using aspartyl protease inhibitors
INVENTOR(S): Ellman, Jonathan A.; Lynch, Gary; Kuntz, Irwin D.; Bi, Xiaoning; Lee, Christina E.; Skillman, A. Geoffrey; Haque, Tasir
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056335	A1	20000928	WO 2000-US7804	20000324
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1178800	A1	20020213	EP 2000-916643	20000324
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539260	T2	20021119	JP 2000-606240	20000324

PRIORITY APPLN. INFO.: US 1999-125958P P 19990324
WO 2000-US7804 W 20000324
OTHER SOURCE(S): MARPAT 133:261535
AB Non-peptide aspartyl protease inhibitors, methods for modulating the processing of an amyloid precursor protein, methods for modulating the processing of a .tau.-protein, and methods for treating **neurodegenerative** diseases are provided.
IT **71732-53-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A61K031-445
ICS A61K031-40; A61K031-16
CC 1-11 (Pharmacology)
Section cross-reference(s): 27
ST aspartyl protease inhibitor **neurodegenerative** disease treatment; amyloid precursor protein processing modulation aspartyl protease inhibitor; tau protein processing modulation aspartyl protease inhibitor
IT Body fluid
Cerebrospinal fluid
Combinatorial library
Nervous system agents
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT Amyloid precursor proteins
Tau factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT Nervous system
(degeneration; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT Brain
(entorhinal cortex; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT Brain
(hippocampus; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.-; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT 9025-26-7, Cathepsin D
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT 54-05-7, Chloroquine **71732-53-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)
IT 211114-74-8P 211114-75-9P 211114-76-0P 211114-94-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 192069-75-3 192069-78-6 192069-80-0 192069-83-3 192069-84-4
192069-91-3 192069-95-7 192069-96-8 192069-98-0 192069-99-1
192070-00-1 211114-70-4 211114-71-5 211114-77-1 211114-78-2
211114-81-7 211114-83-9 211114-84-0 211114-85-1 211114-86-2
211114-87-3 211114-88-4 211114-89-5 211114-90-8 211115-00-3
227031-04-1 227031-05-2 227031-06-3 227031-07-4 227031-08-5
227031-09-6 227031-10-9 227031-11-0 227031-12-1 227031-13-2
296780-76-2 296780-77-3 296780-78-4 296780-79-5 296780-80-8
296780-81-9 296780-82-0 296780-83-1 296780-84-2 296780-85-3
296780-87-5 296780-88-6 296780-89-7 296780-90-0 296780-92-2
296780-93-3 296780-95-5 296780-96-6 296780-98-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 78169-47-8, Aspartyl protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 213458-69-6DP, resin-coupled 213458-69-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

IT 60456-21-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; aspartyl protease inhibitors for modulating processing of amyloid precursor protein and of .tau. protein and for treating **neurodegenerative** disorders)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:449386 CAPLUS
DOCUMENT NUMBER: 131:70860
TITLE: Brain aging assay
INVENTOR(S): Lynch, Gary S.; Bednarski, Eric; Ribak, Charles E.; Gall, Christine M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9934781	A1	19990715	WO 1998-US1140	19980108
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862457	A1	19990726	AU 1998-62457	19980108

PRIORITY APPLN. INFO.: WO 1998-US1140 19980108

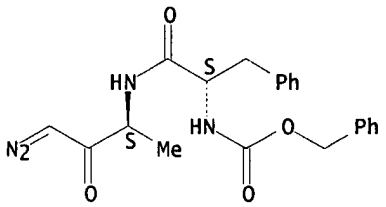
AB Cultured brain slices are treated with a free radical generator, in the presence of a lysosomal enzyme inhibitor (specifically an inhibitor of two cathepsins). The treated brain slices rapidly develop autofluorescent lipofuscin granules - a universal feature of brain aging. Other correlates of the aged brain are also induced by this treatment, thereby providing an in vitro model for (1) the study of brain aging; (2) assessment of anti-brain aging drugs; and (3) therapeutics directed at the clin. condition referred to as **neuronal** ceroid-lipofuscinosis.

IT 71732-53-1
RL: ANT (Analyte); ANST (Analytical study)
(brain aging assay)

RN 71732-53-1 CAPLUS

CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A61K009-44
ICS C12N005-00; C12N005-02; C12Q001-00; G01N001-30; G01N033-48

CC 9-16 (Biochemical Methods)

ST brain aging assay

IT Aging, animal
Animal tissue culture
Brain
Culture media
Cytoplasm
Dendrite (**neuron**)
Drugs
Electron microscopes
Gamma ray
Hypoxia, animal
Lysosome
Mammal (Mammalia)
Neuroglia
Neuronal ceroid lipofuscinosis
Oxidizing agents
Reducing agents
UV radiation
(brain aging assay)

IT Lipofuscins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(brain aging assay)

IT Radicals, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(brain aging assay)

IT Salts, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(brain aging assay)

IT Nerve
(cell body; brain aging assay)

IT Organelle
(granule; brain aging assay)

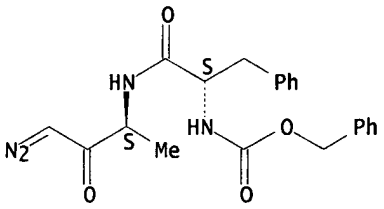
IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; brain aging assay)

IT Nerve
(**neuron**; brain aging assay)
IT Amyloid
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(.beta.-; brain aging assay)
IT 71732-53-1
RL: ANT (Analyte); ANST (Analytical study)
(brain aging assay)
IT 9047-22-7, Cathepsin b 60616-82-2, Cathepsin l
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(brain aging assay)
IT 58-27-5, Menadione 80-15-9, Cumenehydroperoxide 475-38-7, Naphthazarine 4685-14-7, Paraquat 7722-84-1, Hydrogen peroxide, biological studies 9001-37-0, Glucose oxidase 9001-92-7, Protease 9002-17-9, Xanthine oxidase 11062-77-4, Superoxide
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(brain aging assay)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:687413 CAPLUS
DOCUMENT NUMBER: 130:90677
TITLE: Experimentally induced lysosomal dysfunction disrupts processing of hypothalamic releasing factors
AUTHOR(S): Bi, Xiaoning; Pinkstaff, Jason; Nguyen, Kelly; Gall, Christine M.; Lynch, Gary
CORPORATE SOURCE: Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA, 92697-3800, USA
SOURCE: Journal of Comparative Neurology (1998), 401(3), 382-394
CODEN: JCNEAM; ISSN: 0021-9967
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies have shown that exptl. induced lysosomal dysfunction elicits various features of aging in the cortical telencephalon. The present study used cultured slices to test if: (1) it causes similar changes in the hypothalamus, and/or (2) modifies the processing of two releasing factors important to aging. A 2-day exposure to N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone (ZPAD), a selective inhibitor of cathepsins B and L, triggered a pronounced increase in the nos. of lysosomes in the ventromedial and dorsomedial nuclei, and in lateral hypothalamus. Continued incubation with the inhibitor for 3-12 days resulted in the spread of endosomes-lysosomes into dendrites and, in the lateral hypothalamus, the formation of massive, lysosome-filled expansions of **neuronal** processes (meganeurites). These effects did not occur in the arcuate nucleus, making it the first region so far examd. in which lysosomal proliferation is not initiated by hydrolase inhibitors. Despite this, a dense plexus of axons and terminals in the median eminence was partially depleted of growth hormone releasing hormone (GHRH) within 48 h after addn. of ZPAD. Moreover, the inhibitor caused axonal GHRH to become collected into large puncta, an effect highly suggestive of a partial failure in axonal transport. GHRH mRNA levels were not greatly affected by 6 days of ZPAD exposure, indicating that reduced expression did not play a major role in the peptide changes seen at 48 h. Similar but less pronounced immunocytochem. changes were recorded for the somatostatin system in the arcuate and periventricular nucleus. It is concluded that lysosome dysfunction: (1) has different consequences for the arcuate nucleus than other brain regions, and (2) disrupts transport of hypothalamic releasing factors. The potential significance of the results to endocrine senescence is discussed.
IT 71732-53-1
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 2-5 (Mammalian Hormones)
ST lysosome dysfunction hypothalamic releasing factor processing
IT Organelle
(endocytic vesicle; lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT Brain
(hypothalamus, arcuate nucleus; lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT Brain
(hypothalamus, median eminence; lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT Brain
(hypothalamus; lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT Aging, animal
Biological transport
Dendrite (**neuron**)
Lysosome
(lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
IT 9034-39-3, Somatoliberin 51110-01-1, Somatostatin-14
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lysosomal dysfunction induction disrupts hypothalamic releasing factor processing)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:195118 CAPLUS
DOCUMENT NUMBER: 122:3257
TITLE: In vitro embryotoxicity of the cysteine proteinase inhibitors benzyloxycarbonyl-phenylalanine-alanine-diazomethane (Z-Phe-Ala-CHN2) and benzyloxycarbonyl-phenylalanine-phenylalanine-diazomethane (Z-Phe-Phe-CHN2)
AUTHOR(S): Ambroso, Jeffrey L.; Harris, Craig
CORPORATE SOURCE: Department Environmental Industrial Health, Univ. Michigan, Ann Arbor, MI, 48109-2029, USA
SOURCE: Teratology (1994), 50(3), 214-28
CODEN: TJADAB; ISSN: 0040-3709
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

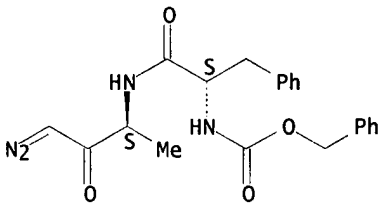
AB This study makes use of whole embryo culture to investigate the potential embryotoxicity of Z-Phe-Ala-CHN2 and Z-Phe-Phe-CHN2, two low mol. wt., active site-directed and irreversible inhibitors of the lysosomal cysteine proteinases. Peptidyl diazomethanes are the most specific inhibitors available for lysosomal cysteine proteinases and can be hypothesized to interrupt visceral yolk sac(VYS)-mediated nutrition during early organogenesis. When added directly to the culture medium of gestational day 10-11 rat conceptuses, both compds. inhibited lysosomal cysteine proteinase activity in the VYS in a concn.-dependent fashion that correlated with the degree of embryotoxicity obsd. Z-Phe-Ala-CHN2 and Z-Phe-Phe-CHN2 were also found to increase the protein content of the VYS, even though all other conceptal growth parameters decreased. This effect was dependent on the serum content of the culture medium and the exposure time. Histol. examn. of Z-Phe-Ala-CHN2-treated conceptuses revealed a dramatic increase in the size and no. of vacuoles in the VYS endoderm epithelium, suggestive of inhibition of VYS proteolysis. At the same time, excessive cell death was obsd. throughout the **neuroepithelium** and in specific regions of the mesenchyme of the corresponding embryos. This cell death manifested morphol. characteristics of apoptosis and could be detected by supravital staining with Nile Blue Sulfate. These findings provide addnl. evidence in support of the hypothesis that lysosomal cysteine proteinases play a crit. role in VYS-mediated histiotrophic nutrition and suggest that peptidyldiazometanes may be useful in further characterization of these enzymes. The possible direct effects of these inhibitors on embryonic cells and the relationships between interruption of VYS-mediated nutritional processes and embryonic cell death are discussed.

IT **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cysteine proteinase inhibitors embryotoxicity)

RN 71732-53-1 CAPLUS

CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 4-6 (Toxicology)

ST embryotoxicity cysteine proteinase inhibitor; benzyloxycarbonyl phenylalanine alanine diazomethane embryotoxicity

IT Apoptosis
Embryo
Lysosome
Teratogenesis
Teratogens
(cysteine proteinase inhibitors embryotoxicity)

IT Deoxyribonucleic acids
Proteins, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(cysteine proteinase inhibitors embryotoxicity)

IT Death
(cell, cysteine proteinase inhibitors embryotoxicity)

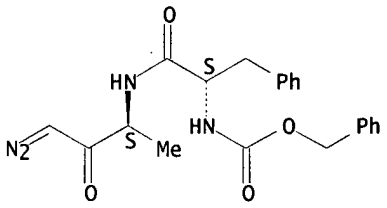
IT 65178-14-5 **71732-53-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cysteine proteinase inhibitors embryotoxicity)

IT 9047-22-7, Cathepsin B 37353-41-6, Cysteine proteinase 60616-82-2, Cathepsin L

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cysteine proteinase inhibitors embryotoxicity)

L35 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:487955 CAPLUS
DOCUMENT NUMBER: 115:87955
TITLE: **Alzheimer**'s disease amyloid .beta.-clipping enzyme (APP secretase): identification, purification, and characterization of the enzyme
AUTHOR(S): Tagawa, kazuhiko'; Kunishita, Tatsuhide; Maruyama, Kei; Yoshikawa, Kazuaki; Kominami, Eiki; Tsuchiya, Takahide; Suzuki, Koichi; Tabira, Takeshi; Sugita, Hideo; Ishiura, Shoichi
CORPORATE SOURCE: Natl. Inst. Neuro sci., Kodaira, Japan
SOURCE: Biochemical and Biophysical Research Communications (1991), 177(1), 377-87
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Alzheimer**'s disease (AD) is the most frequent cause of dementia, although no genetic abnormality has been identified. Recent studies have elucidated the mol. defect in AD, including the abnormal deposition of amyloid .beta. peptide (.beta./A4) in senile plaques of affected individuals. Normal brain contains the enzyme, APP secretase, which cleaves inside the .beta./A4 portion of the precursor protein (APP); abnormal processing of APP occurs in AD brain. Until now, no evidence has been provided that APP secretase is an intracellular proteinase. Two synthetic substrates of APP secretase were prepd., both of which contain the cleavage point and are much more sensitive than substrates previously available to identify APP secretase. Using these substrates, an intracellular proteinase was found that has APP secretase activity. This proteinase has been identified as cathepsin B.
IT **71732-53-1**
RL: BIOL (Biological study)
(cathepsin B inhibition by, kinetics of)
RN 71732-53-1 CAPLUS
CN Carbamic acid, [(1S)-2-[[(1S)-3-diazo-1-methyl-2-oxopropyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 7-2 (Enzymes)
Section cross-reference(s): 14
ST amyloid precursor protein secretase cathepsin B; clipping enzyme amyloid **Alzheimer**; **Alzheimer** amyloid beta clipping enzyme
IT Kinetics, enzymic
(of inhibition, of cathepsin B)
IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(A4, amyloid, pre-, reaction of, with cathepsin B, **Alzheimer**'s disease of human in relation to)
IT 9047-22-7, Cathepsin B
RL: BIOL (Biological study)
(amyloid A4 precursor protein processing by, **Alzheimer**'s disease of human in relation to)
IT **71732-53-1**

RL: BIOL (Biological study)
(cathepsin B inhibition by, kinetics of)